

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference P58920L - PCT	FOR FURTHER ACTION <small>see Form PCT/ISA/220 as well as, where applicable, item 5 below.</small>	
International application No. PCT/GB2004/002849	International filing date (day/month/year) 01/07/2004	(Earliest) Priority Date (day/month/year) 02/07/2003
Applicant BIOFOCUS DISCOVERY LIMITED		

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 10 sheets.

☒ It is also accompanied by a copy of each prior art document cited in this report.

1. Basis of the report

a. With regard to the **language**, the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

☐ The international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).

b. ☐ With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, see Box No. I.

2. ☐ **Certain claims were found unsearchable** (See Box II).

3. ☐ **Unity of invention is lacking** (see Box III).

4. With regard to the title,

☐ the text is approved as submitted by the applicant.

☒ the text has been established by this Authority to read as follows:

PYRAZINE AND PYRIDINE DERIVATIVES AS RHO KINASE INHIBITORS

5. With regard to the abstract,

☐ the text is approved as submitted by the applicant.

☒ the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box No. IV. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. With regard to the drawings,

a. the figure of the **drawings** to be published with the abstract is Figure No. _____

☐ as suggested by the applicant.

☐ as selected by this Authority, because the applicant failed to suggest a figure.

☐ as selected by this Authority, because this figure better characterizes the invention.

b. ☐ none of the figures is to be published with the abstract.

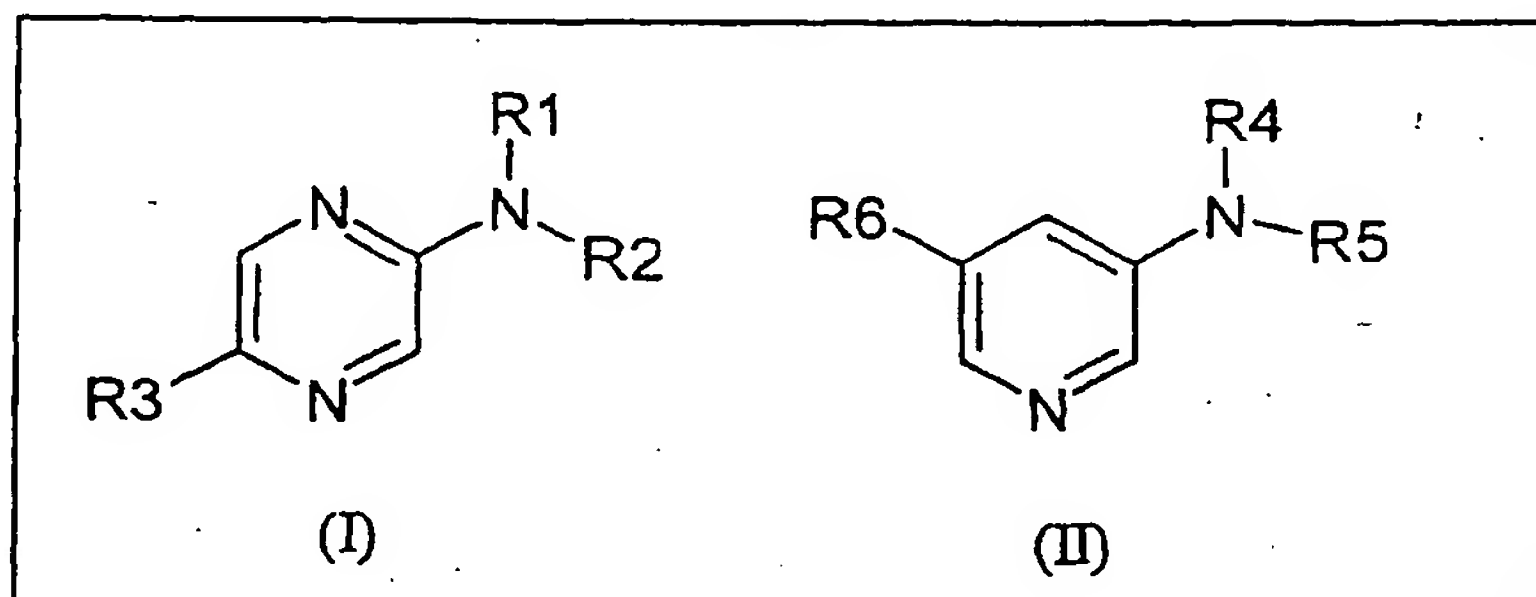
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Box No. IV Text of the abstract (Continuation of item 5 of the first sheet)

The present invention relates to a compound and a group of compounds of formula I and II



with the definitions of R -R according to claim 1 which are inhibitors of Rho kinase (ROK, ROCK). In addition, the invention relates to methods of treatment and use of the compounds in the manufacture of a medicament for application to a number of therapeutic indications including cardiovascular disease (coronary vasospasm, hypertensive disease, arteriosclerosis), stroke, cancer, erectile dysfunction, asthma, osteoporosis, glaucoma and AIDS. The compounds can be used in screening programmes against protein kinases. The invention also provides methods for making compounds and libraries that include these compounds.

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A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C07D405/14 C07D409/14 C07D213/74 C07D241/20 C07D401/14
C07D401/12

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, BEILSTEIN Data, WPI Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 01/17995 A (HUNGATE RANDALL W ; BILODEAU MARK T (US); MANLEY PETER J (US); MERCK &) 15 March 2001 (2001-03-15)	1
A	the whole document	2-20
X	WO 02/24681 A (ORTHO MCNEIL PHARM INC) 28 March 2002 (2002-03-28)	1
A	the whole document	2-20
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☒ Further documents are listed in the continuation of box C.☒ Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search

17 December 2004

Date of mailing of the international search report

26.01.05

Name and mailing address of the ISA

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Von Daacke, A

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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	JEANJOT P ET AL: "N-(alkyl)-2-amino-1,4-pyrazine derivatives: Synthesis and antioxidative properties of 3- and 3,5-p-hydroxyphenyl-substituted compounds" SYNTHESIS, GEORG THIEME VERLAG. STUTTGART, DE, no. 4, 7 March 2003 (2003-03-07), pages 513-522, XP002287849 ISSN: 0039-7881 Table 1, entries 11-17, 24. compounds 13, 15 -----	1, 9
A	WO 02/094814 A (SCHERING AG ; KRUEGER MARTIN (DE); PETROV ORLIN (DE); SIEMEISTER GERHA) 28 November 2002 (2002-11-28) the whole document -----	1-20
A	WO 01/60816 A (AMGEN INC) 23 August 2001 (2001-08-23) the whole document -----	1-20
A	LUMMA W C ET AL: "Piperazinylpyrazines with central serotoninmimetic activity" JOURNAL OF MEDICINAL CHEMISTRY, AMERICAN CHEMICAL SOCIETY. WASHINGTON, US, vol. 21, no. 6, 1978, pages 536-542, XP002287850 ISSN: 0022-2623 abstract; example 3p -----	1-20
P, A	WO 03/099796 A (BU XIANYONG ; CYTOPIA PTY LTD (AU); BURNS CHRISTOPHER JOHN (AU); WILKS) 4 December 2003 (2003-12-04) the whole document -----	1-20
X	WO 03/051366 A (ABBOTT LAB) 26 June 2003 (2003-06-26) Claims; Description; Page 28, Cpd Ib. examples 123, 130 -----	1, 4, 7-20
X	DATABASE CA [Online] CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; BOWMAN, R. E. ET AL: "Preparation and cyclization of 3-aza-1,5-diketones" XP002308867 retrieved from STN Database accession no. 1973:29148 abstract & JOURNAL OF THE CHEMICAL SOCIETY, PERKIN TRANSACTIONS 1: ORGANIC AND BIO-ORGANIC CHEMISTRY (1972-1999), (22), 2878-82 CODEN: JCPRB4; ISSN: 0300-922X, 1972, Compound with RN 39261-80-8 -----	1, 4
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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
E	WO 2004/085409 A (KLING MARCEL ; CHURCH NICOLA (GB); HARRIS JOHN (GB); PROUD ANDREW (GB)) 7 October 2004 (2004-10-07) the whole document -----	1-20
P,A	WO 03/062227 A (PLUEMPE HANS ; HATOUM-MOKDAD HOLIA (US); BOYER STEPHEN (US); DUMAS JAC) 31 July 2003 (2003-07-31) the whole document -----	1-20
P,A	WO 2004/016597 A (LEDFORD BRIAN ; VERTEX PHARMA (US); COCHRAN JOHN (US); GREEN JEREMY (U) 26 February 2004 (2004-02-26) the whole document -----	1,4-20

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Box II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 18 and 19 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

1. ☒ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☒ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box II.1

Although claims 18 and 19 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. claims: 1(part),2,3,6-20(part)

Compounds of formula (I) and related claims

2. claims: 1(part),4,5,6-20(part).

Compounds of Formula (II) and related claims

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Information on patent family members

International Application No

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Patent document cited in search report		Publication date	Patent family member(s)	Publication date
WO 0117995	A	15-03-2001	AU 7351700 A	10-04-2001
			BG 106465 A	29-12-2002
			BR 0013899 A	08-07-2003
			CA 2384101 A1	15-03-2001
			CN 1390215 T	08-01-2003
			CZ 20020861 A3	12-06-2002
			EE 200200123 A	15-08-2003
			EP 1218376 A1	03-07-2002
			HU 0202682 A2	28-02-2003
			JP 2003509342 T	11-03-2003
			MX PA02002559 A	30-07-2002
			NO 20021166 A	25-04-2002
			PL 355639 A1	04-05-2004
			SK 4772002 A3	06-11-2002
			WO 0117995 A1	15-03-2001
			US 2003064996 A1	03-04-2003
			US 2002147203 A1	10-10-2002
			ZA 200201898 A	07-03-2003

WO 0224681	A	28-03-2002	AU 9458401 A	02-04-2002
			CA 2423050 A1	28-03-2002
			EP 1330452 A2	30-07-2003
			JP 2004523474 T	05-08-2004
			WO 0224681 A2	28-03-2002
			US 2003060629 A1	27-03-2003

WO 02094814	A	28-11-2002	DE 10123586 A1	28-11-2002
			WO 02094814 A1	28-11-2002
			EP 1387840 A1	11-02-2004
			JP 2004532248 T	21-10-2004
			US 2004186288 A1	23-09-2004

WO 0160816	A	23-08-2001	AU 3704101 A	27-08-2001
			CA 2400447 A1	23-08-2001
			CN 1429222 T	09-07-2003
			EP 1257546 A1	20-11-2002
			HU 0301117 A2	29-12-2003
			JP 2003532635 T	05-11-2003
			WO 0160816 A1	23-08-2001
			US 2003199534 A1	23-10-2003
			US 2002052386 A1	02-05-2002
			ZA 200206386 A	26-11-2003

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			US 2004235862 A1	25-11-2004
			GB 2392154 A	25-02-2004

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			US 2003199511 A1	23-10-2003
			CA 2470214 A1	26-06-2003
			EP 1463505 A2	06-10-2004
			WO 03051366 A2	26-06-2003

WO 2004085409	A	07-10-2004	GB 2400101 A	06-10-2004
			WO 2004085409 A2	07-10-2004

WO 03062227	A	31-07-2003	CA 2473910 A1	31-07-2003
			EP 1470122 A1	27-10-2004

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Information on patent family members

International Application No

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Patent document cited in search report	Publication date	Patent family member(s)	Publication date
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		US 2004002507 A1	01-01-2004

WO 2004016597 A	26-02-2004	WO 2004016597 A2	26-02-2004
		US 2004106615 A1	03-06-2004
